78. The method of claim 62, wherein said nucleic acid catalyst is a VEGF-R-1 ribozyme.

79. The method of claim 72, wherein the concentration of said lipid is between about 0% and 30%.

80. The method of claim 79, wherein the concentration of said lipid is between about 5% and 30%.

81. The method of claim 80, wherein the concentration of said lipid is about 15%.

82. The method of claim 62, wherein said composition further comprises egg yolk phosphatidyl choline and cholesterol.

83. The method of claim 82, wherein said egg yolk phosphatidyl choline is present at a concentration of about 50%, said cholesterol is present at a concentration of about 25%, said lipid is present at a concentration of about 15%, and said PEG-ceramide conjugate is present at a concentration of about 10%. --

REMARKS

The Invention

The present invention is directed to methods for treating neoplasia in a mammal using formulations comprising PEG-ceramide, a lipid, and a nucleic acid catalyst. Such formulations have been found to be unusually effective in delivering nucleic acid catalysts to neoplastic cells *in vivo*, thereby providing a therapeutic result.

Status

In order to expedite prosecution, original claims 1-61 have been canceled, without prejudice, and replaced with new claims 62-83. In addition, the specification has been

amended to correct the various typographical errors noted in the specification. No new matter has been added to the specification or to the claims with the present amendments.

In the Office Action dated May 27, 1999, the Examiner rejected claims 1-61 under one or more of 35 U.S.C. § 101, § 112, first and second paragraphs, and § 103. Of these, the rejections under § 101, § 112, second paragraph, and § 103 were directed towards composition claims, and the rejections under § 112, first paragraph, were directed towards composition claims and method claims. With entry of the present Amendment, all of the pending claims are method claims directed to the treatment of neoplasia in a mammal. Accordingly, Applicants will limit the present comments to address the rejections concerning the method claims under § 112, first paragraph, as if they were directed towards the presently pending claims. Applicants believe that the rejections under § 101, 112, second paragraph, and §103 have been obviated by the present amendment, and thus will not address these rejections.

Support for the Present Amendments

Support for the present amendments can be found throughout the specification and claims as originally filed. All of the amendments to the specification simply serve to correct typographical errors. Support for new claims 62 and 63 can be found, *e.g.*, in original claims 27, 28, 31, and 32, and at page 7, line 30 to page 8, line 1. Support for new claim 64 can be found, *inter alia*, at page 7, lines 19-21, and in original claim 47. Support for new claims 65 can be found, *e.g.*, in original claims 30 and 34. Support for new claim 66 can be found, *e.g.*, in original clam 2. Support for new claim 67 can be found, *e.g.*, in original claim 15. Support for new claim 68 can be found, *inter alia*, in original claim 3. Support for new claim 69 can be found, *e.g.*, in original claim 3. Support for new claim 70 can be found, *e.g.*, in original claim 5. Support for new claim 71 can be found, *inter alia*, in original claims 6 and 7. Support for new claim 72 can be found, *e.g.*, in original claim 9. Support for new claim 73 can be found, *e.g.*, in original claims 10 and 11. Support for new claims 74-76 can be found, *e.g.*, in original claims 12-14, respectively. Support for new claim 77 can be found, *e.g.*, in original claim 36. Support for new claim 78 can be found, *e.g.*, in original claim 37. Support for new claims 79-81 can be found, *inter alia*, in original claims 42-44, respectively. Support

for new claims 82 and 83 can be found, *e.g.*, in original claim 45. No new matter has been added.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 27-34 were rejected under 35 U.S.C. §112, as allegedly nonenabled by the specification as originally filed. Specifically, the Examiner asserts that the present specification does not enable claims directed to methods of treating a human disease such as cancer using the claimed formulations. Applicants respectfully traverse this rejection.

One of skill would have had no difficulty making and using the claimed invention

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without undue experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. Applicants assert that, in the present case, this requirement is easily met by the specification as filed.

The present claims are directed to methods for treating a neoplasia in a mammal. These methods involve administering to the mammal a composition comprising a PEG-ceramide, a lipid, and a nucleic acid catalyst. Using these methods, the nucleic acid catalyst is delivered to neoplastic cells in the mammal and a therapeutic effect is achieved. Applicants assert that the present application provides extensive teaching regarding how to carry out each step of the claimed methods, and thus easily meets the enablement requirement as defined by the Federal Circuit and as set forth in the MPEP.

The specification provides substantial teaching regarding how to make the claimed formulations. For example, suitable lipids are described, *inter alia*, at page 16, line 22 to page 18, line 6; PEG-ceramide conjugates are described, *e.g.*, at page 18, lines 7-15; proportions for combining PEG-ceramide and lipids are found, *inter alia*, at page 18, line 16 to page 19, line 8; methods of formulating the compositions are provided, *e.g.*, at page 19, line 27 to page 22, line 3; and suitable nucleic acid catalysts are provided, *e.g.*, at page 22, line 6 to page 27, line 30. In addition, Examples 1 and 2, found at pages 29, line 10 to page 30, line 24,

provide working examples of the preparation of the PEG-ceramide, lipid, and nucleic acid catalyst formulations.

In addition, the specification teaches the administration of the formulations to a mammal, including a mammal with a neoplasia. For example, suitable pharmaceutical compositions are taught, *e.g.*, at page 27, lines 2-13, and at page 27, line 29, to page 28, line 23. In addition, systemic administration of the compositions is taught, *e.g.*, on page 27, lines 14-28, and methods of determining a pharmaceutically effective dose are taught, *e.g.*, at page 28, lines 23-31. Further, numerous Examples are provided that teach the administration of the formulations to mammals, and demonstrate the stability, tumor cell targeting, and ability of the formulations to inhibit the growth of tumors *in vivo*. *See, e.g.*, Examples 3-6, found at page 30, line 25 to page 35, line 29.

In view of the above, Applicants respectfully assert that the specification provides ample teaching regarding how to make and use the claimed invention, and, consequently, one of skill in the art would have been fully enabled to make and use the claimed invention at the time of the filing date.

Operability of claimed invention

In view of the extensive teaching, discussed above, regarding ***how*** to make and use the present invention, Applicants interpret the Examiner's § 112, first paragraph rejection as relating in essence to the ***utility*** of the claimed invention, *i.e.*, whether the invention actually works as claimed. As stated in the Office Action, "[o]ne of skill in the art would not accept on its face ***the successful delivery,*** and further treatment effects of the claimed catalyst compositions in whole organisms other than mice, in view of the lack of guidance in the specification and the unpredictability in the art." *See*, pages 10-11 of the Office Action (emphasis added). As discussed below, Applicants respectfully assert that, first, it is improper to base an "operability rejection" on § 112, first paragraph alone, and that, second, the Examiner has failed to establish grounds for questioning the operability of the invention. In addition, the specification as filed provides ample evidence that the claimed invention is fully operable.

Although an inoperable invention cannot be enabled under § 112, first paragraph, a proper rejection on the basis of utility must be made under 35 U.S.C. § 101, or under § 101 and §112, but not §112 alone. As stated in the MPEP:

> The examiner should make ***both rejections*** (i.e., a rejection under 35 U.S.C. 112, first paragraph, ***and*** a rejection under 35 U.S.C. 101) where the subject matter of a claim has been shown to be nonuseful or inoperative....In other words, Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper. In particular, the factual showing needed to impose a rejection under 35 U.S.C. 101 ***must be provided*** if a 35 U.S.C, 112, first paragraph, rejection is to be imposed on "lack of utility" grounds. (*See*, MPEP § 2164.07) (emphasis added).

In the present case, the Examiner has made no such rejection under § 101 regarding the alleged inoperability of the claimed invention. Thus, the present § 112, first paragraph, on the grounds of alleged lack of utility is improper.

Further, even if a proper rejection under § 101 had been set forth, Applicants respectfully assert that the Examiner has failed in the present case to provide a reasonable basis to question the operability of the invention. The Examiner is reminded that, if he believes a rejection is appropriate on the basis of inoperability, under § 101 or § 112, he has the burden of providing a reasonable basis for his conclusion:

> When the examiner concludes that an application is describing an invention that is nonuseful, inoperative, or contradicts known scientific principles, ***the burden is on the examiner to provide a reasonable basis to support this conclusion***. Rejections based on 35 U.S.C. 112, first paragraph and 35 U.S.C. 101 should be made. *See*, MPEP §2164.07 (emphasis added).
>
> To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) ***make a prima facie showing*** that the claimed invention lacks utility, and (B) ***provide a sufficient evidentiary basis*** for factual assumptions relied upon in establishing the *prima facie* showing. In re Gaubert, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975) ("Accordingly, the PTO must do more than merely question the objective truth of the statement of operability.") If the Office cannot develop a proper *prima facie*

> case and provide evidentiary support for a rejection under 35 U.S.C. 101, a rejection on this ground should not be imposed. *See*, MPEP §2107.01 IV (emphasis added).

Applicants respectfully assert that, in the present case, the Examiner has failed to meet this burden as mandated in the MPEP. Specifically, in setting forth the rejection under § 112, first paragraph, the Examiner has pointed to four alleged sources of unpredictability in delivering nucleic acids using liposomal formulations. As discussed below, Applicants assert that none of these alleged sources of uncertainty apply in the present case.

The first alleged source of uncertainty cited by the Examiner is:

> (1) stability of the ribozyme liposome composition *in vivo* in any whole organisms other than mice.

Applicants remind the Examiner that the case law is clear that a demonstration of efficacy in experimental animals is more than sufficient to establish utility for broad claims for an invention under 35 U.S.C. § 112. For example, in *In re Jolles*, 206 USPQ 885 (CCPA 1980), the CCPA stated that:

> This court recognizes 'that a demonstration that a compound has desirable or beneficial properties in the prevention, alleviation, or cure of some disease or manifestation of a disease in experimental animals does not necessarily mean that the compound will have the same properties when used with humans.' ***However, this is by no means support for the board's position that such evidence is not relevant to human utility.***
>
> To the contrary, this court has accepted tests on experimental animals as sufficient to establish utility.... *Id.* at 890 (citations omitted; emphasis added).

Thus, the demonstration that the present formulations are effective in mice is more than sufficient to establish utility in whole organisms other than mice. It is important to note that the Court's position in this regard recognizes the essentially universally held position among scientists that work in experimental mammals is of critical importance and relevance to other mammals, including humans. Even a reference cited by the Examiner regarding this

point, *i.e.*, Crystal (1995), clearly accepts the importance of research in mice, and simply points out that, occasionally, predictions based on work in mice do not prove true in humans. As stated by Crystal:

> *Humans are not simply large mice.* There have been several ***surprise examples***, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials. (Crystal, page 40; non-bold italics in original, bold italics added).

This is entirely consistent with the above-described position of the CCPA, *i.e.*, that work in mice has great predictive value in determining efficacy in other animals, such as humans. The fact that, occasionally, "surprise examples" arise in which these predictions are not borne out in no way detracts from the value of this work or from the reasonable expectation of success that scientists have in extrapolating from work performed in experimental animals to other animals.

Applicants emphasize that this issue is of great importance, because it relates to the fundamental aims of the patent laws themselves. As stated by the Federal Circuit in *In re Brana*, 34 USPQ2d 1436, (Fed. Cir. 1995):

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *Id.* at 1442-1443.

Thus, providing patent protection for a discovery based on work in experimental animals provides an important and often required incentive for continued research and development.

Finally, Applicants assert that this alleged source of uncertainty lacks scientific credibility. There is no reason to believe that the increased stability seen in mice would not

also be seen in other mammals, including humans, and the Examiner offers no scientific explanation to support this objection. Applicants point out that the specification provides ample teaching for the administration of the claimed formulations to any animal, not just mice. Thus, the present claims can be applied to any animal without undue experimentation.

The second alleged source of uncertainty is:

> (2) effective delivery to the whole organism and specificity to the target tissues

As discussed *supra*, the specification as filed provides extensive teaching regarding how to prepare and administer the claimed formulations to whole organisms. In addition, the data presented in the Examples section demonstrates that, using the claimed formulations, nucleic acid catalysts can be delivered with increased stability and targeting to target tissues, such as tumor cells and retinal cells. For example, the specification shows that the claimed formulations provide increased levels of intact ribozyme in plasma and in target tissue compared to other formulations (*see*, for example, Examples 3, 4, and 5). Thus, the data provided in the application demonstrates that this alleged source of unpredictability has been overcome.

The third alleged source of uncertainty cited by the Examiner is:

> (3) dosage and toxicity

Applicants point out that the specification as filed provides substantial teaching regarding proper dosage of each component of the formulations. For example, the section from page 18, line 16 to page 19, line 8, provides preferred ranges of concentrations of non-cationic lipids, cationic lipids, PEG-ceramide conjugates, and cholesterol. In addition, page 29, lines 21-29 provide preferred dosage ranges for pharmaceutical administration of active ingredients, *e.g.*, ribozymes.

Further, the Examples section provides a demonstration that the claimed formulations can be delivered to whole organisms, *i.e.*, mice, at a dosage that is effective for

reducing tumor growth, but in the absence of toxicity. Thus, this potential source of uncertainty has clearly been overcome by the present invention.

Finally, the Examiner alleges a fourth source of uncertainty:

> (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects via the catalytic molecule.

With respect to this fourth point, Applicants point out, again, that the specification provides conclusive evidence that the claimed formulations provide increased delivery of the nucleic acid catalysts to cells *in vivo*, *e.g.*, to tumor cells as shown in Example 5. Further, Example 6 shows that the claimed formulations, when used to deliver ribozymes against VEGF-R-1, lead to a ***dramatic inhibition in the growth rate of tumors*** in mice. Applicants assert that this result in itself represents the ultimate demonstration of "desired treatment effects."

In view of the above, Applicants respectfully assert that none of the potential sources of uncertainty raised by the Examiner apply to the present invention. Applicants submit that, instead, the evidence provided in the specification demonstrates that the claimed formulations have overcome these potential sources of difficulty, and, indeed, their ***demonstrated success*** in delivering nucleic acids to target cells *in vivo* ***is the basis of the invention***.

Finally, Applicants point out that this demonstrated connection between neoplasia and PEG-ceramide, lipid, and nucleic acid catalyst formulations, as shown in the specification for VEGF-R-1 ribozymes, can be made with any ribozyme directed against any RNA associated with neoplasia, in humans or other animals. In this regard, Applicants note that the central aspect of their invention is that a nucleic acid catalyst, of any identity, can be delivered to neoplastic cells *in vivo*. Applicants have used an exemplar ribozyme, VEGF, to demonstrate increased stability and cellular targeting *in vivo* using the claimed formulations. This increased stability and cellular targeting, however, does not depend on the sequence or activity of the nucleic acid catalyst included in the formulation.

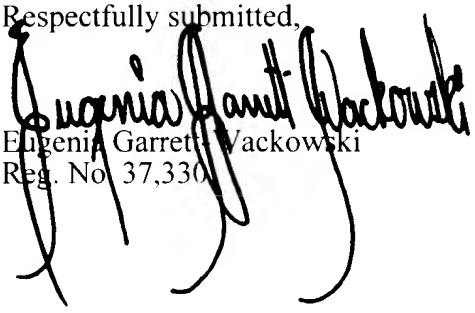
In view of all of the above, Applicants assert that new claims 62-83 are fully enabled by the specification under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejections under § 112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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